Remarks

Claims 1-7, 9-25 and 27-54 are pending in the application. Claims 1-19, 24, 25, 27-33 and 48-54 are allowed. Claims 20-23 and 34-47 stand rejected. Claims 14, 17, 18 and 27 are objected to. Claims 20, 21 and 34-39 have been amended herein. Reconsideration is respectfully requested in view of the following comments.

As a preliminary matter, Applicants thank the Examiner for her telephone discussion of the Final Office Action with Thomas Sossong, Applicants' representative, on June 28, 2006. It is Applicants understanding that the Examiner and Dr. Sossong discussed potentially allowable subject matter, and that the treatment of "inflammation" with compounds of the invention was specifically discussed and identified by the Examiner as potentially allowable subject matter.

Response to Objection to Claims 14, 17, 18 and 27 for Improper Claim Format

The Examiner has objected to the amendment submitted on January 17, 2006, as being in improper format. Specifically, the Examiner asserted that in accordance with 37 C.F.R. § 1.173, the claims listed in an amendment filed during a reissue examination must be relative to the original patent claims. Applicants have made the correction to claims 14, 17, 18 and 27 as suggested by the Examiner, and accordingly, the claim listing set forth herein properly reflects the claim amendments relative to the original patent claims. No new matter has been added by way of these amendments, which merely correct clerical errors of formatting.

Response to Rejection under 35 U.S.C. § 112, first paragraph

Claims 20-23 and 34-47 were rejected pursuant to 35 U.S.C. §112, first paragraph, as allegedly lacking enablement. Applicants respectfully disagree, particularly in view of the claim amendments set forth herein, and submit that claims 20-23 and 34-47 are enabled under 35 U.S.C. § 112, 1st paragraph, for the reasons set forth below.

As a preliminary matter, Applicants have canceled claims 22-23 and 40-41, rendering the Examiner's rejection of these claims moot.

Applicants note that the Examiner has once again indicated that the specification is "enabling for treating inflammation," and has now also indicated that the specification

is enabling for treating colon cancer, prostate cancer, breast cancer, brain cancer, lung cancer, pancreatic cancer, and bladder cancer. The Examiner has also stated, on page 8 of the Office Action, that the methods are enabled for the treatment of the specific cancers which have been set forth in the Reddy Declaration or for which Applicants have provided references.

Without prejudice to inclusion of any subject matter in any later-filed or copending applications, Applicants have amended claims 20 and 34-36 to more specifically point out that the claimed methods of treating cyclooxygenase-mediated disorders encompass those disorders for which the Examiner has indisputably indicated Applicants are enabled. Specifically, the claims have been amended to recite that the method of treatment is directed to those cancers that have been set forth in the Reddy Declaration or for which Applicants have provided references. Support for these amendments can be found throughout the specification, and in particular, in column 12, from line 26 through line 55.

Applicants have amended claims 21 and 37-39 to more specifically point out that the claimed methods of treating cyclooxygenase-mediated disorders encompass those disorders for which the Examiner has indicated Applicants are enabled in the telephone conversation of June 28, 2006, with Thomas Sossong, Applicants' representative. Specifically, claims 21 and 37-39 have been amended to recite the treatment of "inflammation" according to the present invention. Support for the treatment of inflammation using compounds of the invention can be found in the specification from line 51 in column 11 through line 25 of column 12.

The test of enablement is not whether *any* experimentation is necessary, but whether, if experimentation is necessary, it is undue. MPEP §2164.01 (citing *In re Angstadt*, 537 F.2d 498, 504 (C.C.P.A. 1976)). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. *Id.* Further, the specification need not disclose what is well-known to those skilled in the art and preferably omits that which is well-known to those skilled and already available to the public. MPEP §2164.05(a) (citing *In re Buchner*, 929 F.2d 660, 661 (Fed. Cir. 1991)).

The state of the art at the time of filing of the present Application includes a considerable amount of literature disclosing therapeutic potential of cyclooxygenase inhibitors, particularly COX-2 inhibitors, in treating tumors that express cyclooxygenase. See, for example, Gupta *et al.* (PMID:10579801, abstracting *Prostate*; 2000, 41(1); page 73-78) which states, "Aberrant or increased expression of cyclooxygenase (COX)-2 has been implicated in the pathogenesis of many diseases including carcinogenesis. COX-2 has been shown to be over-expressed in some human cancers." Gupta's analysis of data for COX-2 expression in prostate tissue showed utility of COX-2 inhibitors "for prevention or therapy of prostate cancer in humans." See also, Yip-Schneider *et al.* (PMID:10657949 abstracting *Carcinogenesis*, 2000, 21(12), page 139-46) which states, "COX-2 expression is up-regulated in several types of human cancers and has been directly linked to carcinogenesis." Yip-Schneider evaluated the role of COX-2 in pancreatic cancer and concluded that "COX-2 may play an important role in pancreatic tumorigenesis and therefore be a promising chemotherapeutic target for the treatment of pancreatic cancer." See also Ochaia *et al.* (PMID: 10665651, abstracting *Jpn. J. Cancer Res.*, 1999, 90(12), page 1338-43). Based on known COX-2 expression in various human cancers, Ochaia investigated COX-2 expression in non-small cell lung cancers (NSCLC) and concluded that "COX-2 may be associated with carcinogenesis of NSCLC, and that it may be a target for the treatment of NSCLC." See also Komhoff *et al.* (PMID 10880372, abstracting *Am. J. Pathol.*, 2000, 157(1), page 29-35). Komhoff states that, "Studies in human and animal models have shown that COX-2 is up-regulated in several epithelial carcinomas including colon, breast, and lung." Komhoff investigated COX-2 involvement in human bladder cancer and demonstrated "elevated expression of COX-2 in a high percentage of high-grade bladder carcinomas, suggesting a possible role of COX-2 in the progression of bladder urothelial carcinoma and supporting its potential as a therapeutic target in human bladder carcinoma."

The references above (PubMed Abstracts submitted as "Exhibit 1" with the previous response filed by Applicants on January 17, 2006) demonstrate that the state of the art includes recognition that tumors expressing a cyclooxygenase respond to treatment with a COX-2 inhibitor. The references further show that determination of

cancers that express COX-2 constituted experimentation that did not rise above a level that was routine in the art.

By way of example, Applicants respectfully point out that the disclosure of U.S. Patent No. 5,972,986, which was incorporated by reference in its entirety into the present application, demonstrates the successful treatment of a cancerous tumor using a COX-2-specific inhibitor. Specifically, column 12 in patent 5,972,986 describes the treatment and shrinkage of a tumor in a mammal by treatment of the tumor with a COX-2-specific inhibitor. Therefore, the treatment of COX-2-mediated conditions and diseases with COX-2-specific inhibitors was well-established at the time of filing of the present application, and such treatment is well within the ability of the ordinary skilled artisan.

Applicants also refer the Examiner to the Declaration under 37 C.F.R. § 1.132 by inventor M.V. Ramana Reddy (the "Declaration"). This Declaration, submitted with the previous response filed by Applicants on January 17, 2006, presents post-filing data that demonstrates a further reduction to practice of the invention claimed and set forth in the as-filed application. In particular, paragraph 6 of the Declaration illustrates the inhibitory effect of compounds of the invention on cancer cells from various sources, including colon, breast, brain, and prostate.

Applicants further refer the Examiner to U.S. Patents No. 5,604,253 and 5,908,852, submitted herewith (hereinafter, "the '253 patent" and "the '852 patent," respectively). The '253 patent and the '852 patent demonstrate that the state of the art of treating inflammation with a COX-2 inhibitor includes recognition that inflammation associated with cyclooxygenase activity responds to treatment with a COX-2 inhibitor. For example, Applicants direct the Examiner's attention to the Experimental Examples in the '852 patent (columns 24 through 27), which illustrate the biological treatment of inflammation using a COX-2 inhibitor. These two patents further show that determination of inflammation associated with cyclooxygenase activity constituted experimentation that did not rise above a level that was routine in the art.

Accordingly, Applicants respectfully submit that claims 20, 21 and 34-39 are enabled, and request that the rejection of the claims be reconsidered and withdrawn in view of the amendments and arguments set forth above.

Conclusion

Based on the foregoing, all pending claims are believed in condition for allowance. An early and favorable action toward that end is earnestly solicited.

Respectfully submitted,

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By _____

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